With the Author's Compliments

15

SUMMARY OF THREE LECTURES

ON

TRANSFUSION:

ITS

PHYSIOLOGY, PATHOLOGY, AND PRACTICE.

Delivered at the Royal College of Surgeons.

BY

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LECTURE I.

Introductory.

The first real advance in our knowledge of the physiology of transfusion was made when Leacock in 1817 and Blundell in 1825 drew attention to the marked difference in the result, according as the blood transfused was obtained from an animal of the same species—"similar" blood, or from an animal of another species—"dissimilar" blood. The later researches of Panum, Ponfick, Landois, and others fully established that this difference was due to the poisonous action of the hæmoglobin of dissimilar blood on the organism. The investigations made in recent years have, therefore, had reference more particularly to the behaviour of similar blood, and the fate of its different elements—corpuscles, hæmoglobin, organic constituents of the plasma—after transfusion. As the result of these, much light has been thrown on many important points connected with the physiology and pathology of transfusion; on the importance of proper oxygenation of the blood by Bischoff and Brown-Séquard; on the differences between pure blood and blood after defibrination, and the relative advantages of each for purposes of transfusion by Dumas and Prévost, Martin, Panum, Ponfick, Landois, Hayem, von Ott, Armin Köhler, and others; on the fate of the red corpuscles after transfusion by Panum, Worm-Müller, Hayem, von Ott, myself, and others; on the fate of the organic constituents of the transfused blood by Worm-Müller, Lesser, Tschiriew, and Forster; and, lastly, on the physical properties of transfused blood and of saline solutions by Kronecker and Sander, Schwarz, von Ott, Maydl, and many others.

Nevertheless, the question as to the value of transfusion seems ever to remain an open one, and still retains its interest both for the lay and for the medical mind. The present attitude of medical opinion may be described as one of healthy scepticism. The advocacy of transfusion is left in the hands of a few; and the frequency with which one meets with descriptions of new instruments instead of reports of successful cases may be regarded as lending some colour to the suspicion that even in the minds of these few there is some lurking doubt as to the safety or value of the operation. Much of this hesitancy is traceable to two circumstances. First, that after taking all due precautions, the operator feels himself liable at any moment to be confronted with certain dangers of whose nature he has but imperfect knowledge, and which he is, therefore, not in a position to avoid or confidently grapple with. Secondly, that even when these have been avoided or overcome he is, to a great extent, ignorant of the

rationale of the operation ; he is ignorant how far or in what way his interference has contributed to the result, even when successful ; and he cannot explain why the operation fails under conditions that, so far as he can judge, are equally favourable to success.

The problems presented by a study of transfusion are thus partly physiological, partly pathological. The physiological problem is to determine the fate of the different elements of the transfused blood, and to ascertain the functions they severally or collectively discharge in the body of their host. A knowledge of these is essential whether the operation of transfusion is to be advocated or rejected. The pathological portion of the problem is to explain the nature of the disturbances, such as dyspnœa, violent action of the heart, tendency to syncope, and other symptoms, objective and subjective, frequently presented by the patient during the performance of the operation.

Lastly, there always remains the important practical question, What is the value of transfusion and in what conditions is its performance indicated? The answer to this question implies a knowledge of the nature of the changes in the blood in disease, and it is this portion of the problem of transfusion which has hitherto received an attention altogether inadequate to its real importance.

Physiology of the Blood.

Attention was then directed to some points connected with the physiology of the blood, a knowledge of which is essential to a right understanding of the principles on which transfusion is based.

The ground idea of transfusion is that we are replacing a structure incapacitated by loss or disease for the discharge of its functions by one of similar nature, presumably capable of taking up these functions.

What are the functions of the blood in health, and how is it fitted by structure or composition to discharge them ?

The physiology of the blood presents problems of peculiar difficulty, arising from its fluid nature and its close relation to all other tissues of the body—a relationship peculiar to it alone. What is the behaviour of the blood under such circumstances? Its quantity and quality appear to be constantly varying. Are we then entitled to regard it as a tissue at all, seeing that it apparently has no stable composition? When we speak of the blood, do we speak not so much of a tissue as of a mass of fluid of varying quantity and quality, holding certain corpuscular elements in suspension, and presenting merely a certain average composition in virtue of the united action of all the tissues? Unlike all other structures to which we give the name of "tissue," it appears to possess no single characteristic property, its composition being determined solely by the quantity and quality of the material poured into it by the various tissues. Hence it is considered "far more profitable, indeed necessary, to treat of the blood, not as a tissue by itself but as the great means of communication of material between the tissues properly so called" (Foster). It is usual to regard it as a mass of material by which the tissues are bathed. Hence the title frequently given to it of "the nutritive fluid of the tissues."

To regard the blood in this light seems reasonable enough in health, where we have to do with a certain average activity of all the organs of the body. Even as a working hypothesis—and it is as such that this view chiefly recommends itself—this view com-

pletely breaks down in the presence of the far more difficult problems presented by the blood in disease. So far from the blood being a mixture of water, proteids, carbohydrates, fats, etc.—from being "the nutritive fluid of the tissues,"—a consideration of all the evidence afforded by a study of its behaviour in health and disease points irresistibly to the conclusion that it is no more the "nutritive fluid" than it is the "respiratory fluid" of the tissues. In both cases alike the material, whether gaseous or solid, contained in the blood and used up by the tissues is in the blood simply in virtue of its carrying function—is in the blood simply in course of transit to the tissues.

The most remarkable feature presented by the blood is not, as is usually supposed, its varying composition, but the remarkable power it possesses of maintaining a composition as rightly entitled to be termed stable as that of any other tissue of the body, and that notwithstanding that its close relation to all the other tissues renders it peculiarly subject to such changes.

The evidence pointing to this conclusion is of a twofold kind: (1) that derived from a study of the behaviour of the blood both in health and disease, under conditions tending to alter its composition both in quantity and quality; (2) that derived from a study of the nature and composition of the plasma.

The former evidence—functional evidence—shows that the blood possesses one of the most characteristic properties of living tissues, namely, great irritability; evidenced in its case by its intolerance of the presence of bodies, even those normally present in it, such as water, sugar, peptones, salts, that do not reach it by the ordinary channels, or that reach it in too great quantity, even by the ordinary channels.

The latter evidence—structural evidence—goes to show that not only in the corpuscles, but also in the plasma, we have to do with proteid material built up into organised form, and differing from the proteid material introduced into the blood from the food.

The key to the solution of the problems presented by the blood, both in health and disease, is to be found in the recognition of this fact, that what are termed changes in its composition are in the great majority of instances merely changes in virtue of its function as the carrying tissue of the body. A clear distinction is to be drawn between changes in the blood as a tissue—structural changes—and changes in virtue of function—functional changes. The latter, however marked—sugar in diabetes, uric acid in gout—do not constitute disease of the blood; the former, however slight—deficiency in hæmoglobin, in the number of corpuscles, etc.—do constitute disease, and their cause must always be sought, not in the tissues as a whole, but in certain organs specially concerned in the fate of the blood, the so-called blood-organs.

The conclusions arrived at from a study of the behaviour of the blood in health and disease were the following:

1. That the blood is in all respects a living tissue of highly specialised structure, adapted for the performance of certain specialised functions—namely, the conveyance of food material, gaseous and solid, to all the tissues of the body.

2. That it possesses, in common with all tissues, the power which is the characteristic feature of living tissue—the power, namely, of maintaining a certain physical structure and a certain chemical composition in the presence of the most varying physical conditions.

3. That the peculiar fluid nature of its matrix necessitates in its case special arrangements for the regulation of its composition not required by the other tissues.

4. That this mechanism is to be found partly in itself—its white corpuscles and the endothelium of its capillary walls—partly in certain organs in specially close relation to the blood, which are so situated that its composition even as a carrying tissue is regulated at certain convenient points in the circulation—namely, gastro-intestinal mucous membrane, more especially the follicular tissue around the portal radicles, the spleen, liver, bone-marrow, and lymphatic glands. With the exception of the latter, all these blood-organs possess in varying degree certain features more or less common to them all—namely, (1) slowness of circulation—common to all; (2) closeness of relation of cells to the blood—spleen and bone-marrow; (3) power of accommodating large and varying quantities of blood, chiefly venous, which the portal system, including the spleen, possesses in special degree.

Physiology of Transfusion.

Nutritive Properties of Blood.—In transfusing blood we are thus transfusing a living tissue presumably capable of carrying on all the functions of healthy blood. It is necessary now to consider more particularly what these are; and, first of all with regard to the nutritive properties so generally ascribed to the blood.

In Health.—Any nutritive value the blood may have must depend on the presence of its proteid constituents. Of these the blood contains about 20 per cent., distributed unequally between the corpuscles and the plasma, rather more than 15 per cent. being contained in the corpuscles, rather less than 5 per cent. in the plasma.

How is the blood affected in starvation? As the so-called "nutritive fluid of the tissues," does it suffer in any special degree at a time when the waste of the tissues is not being replaced by food material from without? We know that, under such circumstances, the loss of substance does not affect all tissues equally. Some, as the heart muscle and the brain, suffer but little; others, as the muscles, generally lose much. Does the blood become poor in albuminous constituents out of all proportion to the loss in the other tissues, as might be expected if its substance is in the first instance used up as food? On the contrary, the observations of Voit, Panum, and Heidenhain show that the loss in weight of the blood is proportional to the general loss in weight of the tissues generally, and that the proportion of its various constituents remains unaltered. In starvation, as in health, the blood suffers quantitatively and qualitatively as other tissues. It behaves, not as a mass of nutritive material, but as a tissue. Its carrying function, nutritive and respiratory, remains the same to the last. The fact that some tissues, such as skeletal muscle, suffer much, while others, such as the heart muscle, functionally active to the very last, lose but little in weight, implies that the latter must have been nourished at the expense of the former; that food material must have been conveyed by the blood from the muscles to the heart. The nutritive function which the blood thus subserves in virtue of its carrying function remains the same as in health. The same holds true of its respiratory function. Lastly, the quantity of blood never falls below the point at which the circulation is unable to be maintained; so that the great function of circulation which the blood is enabled to discharge in virtue of its physical properties—volume, viscosity, etc.—remains unaffected.

After Transfusion.—Since the blood has no nutritive value in itself in health, apart from the material it carries, we should

hardly expect it to have any after transfusion. Nevertheless, it is one of the many properties claimed for transfused blood that, even if it be destroyed, it may subserve some purpose of nutrition in the organism.

Any nutritive value the blood may have must depend on the presence of its proteid constituents. Now, the one fact definitely established with regard to the fate of proteids introduced as food by the ordinary channels is that their utilisation as food by the tissues implies their breaking up in the first place, and the excretion from the body of a quantity of nitrogen, chiefly in the form of urea, closely corresponding to the amount contained in the food. No such process is known in the body as a building up without a breaking down. Anabolism and catabolism always go hand in hand.

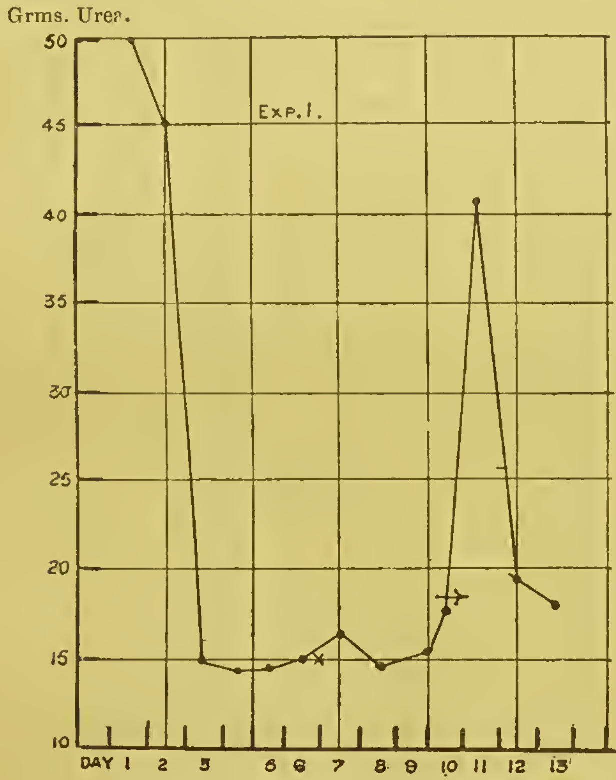

Fig. 1. × =394 grm. Blood transfused (15.06 grm. Nitrogen).
+ =375 grm. Meat by the Mouth (12.75 grm. Nitrogen).

If to an animal in a state of starvation—whose excretion of nitrogen is entirely at the expense of its own tissues, and after a time remains fairly constant—we give a certain amount of proteid material as food, we might expect that the greater part of the material thus given would be built up into the tissues and but little be excreted. What we do find, however—as will be seen by reference to the accompanying charts, in which I have represented graphically the results obtained by Forster in his experiments—is that the whole of the nitrogen thus introduced is excreted from the body at once; there is an increased excretion of nitrogen corresponding to the quantity given in the food.

If to an animal in a similar condition a certain quantity of blood be given by the mouth, we have a similar result; the

increased excretion of nitrogen corresponds to the quantity of nitrogen in the blood administered. Thus, Tchiriew found that, in a period of three days, during which 13.19 grammes of nitrogen were given in the form of blood by the mouth, the excretion was 14.55 grammes; in another period of three days, the excretion was 14.43 grammes as compared with 14.38 grammes in the food; in a third period, the excretion was 15.42 grammes as compared with 15.28 in the food.

The proteid material, whether in the form of meat or in the form of blood, had undergone disintegration; its nutritive value corresponded to the quantity of nitrogen it contained, and was expressed by the excretion of nitrogen after its administration.

Very different is the result after transfusion, when the blood is introduced directly into the vessels instead of by the mouth. As

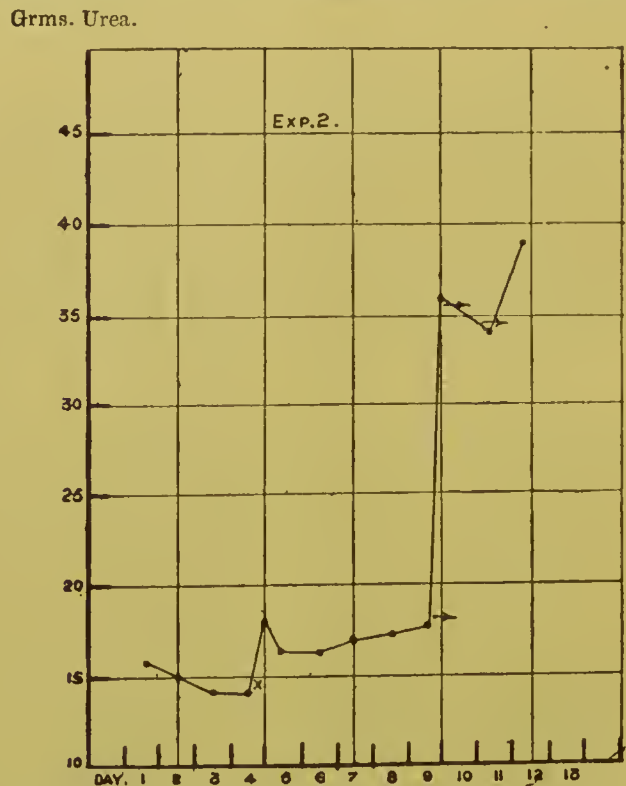

Fig. 2. × =611 grm. Blood transfused (19.92 grm. Nitrogen).
→ =600 grm. Meat by the Mouth.

will be seen (Figs. 1 and 2), there is little or no increase in the nitrogen excreted. Some slight increase there always is, but it in no way corresponds to the quantity of nitrogen contained in the injected blood. Thus, of 19.09 grammes of nitrogen in the blood transfused, only 6.85, and of 18.53 thus given only 10.60, of 7.84 only 4.39 grammes appeared in the urine in the periods over which the transfusions were made.

We must conclude, then, that blood transfused is not immediately destroyed, and its nutritive value is therefore correspondingly less than the same quantity of blood given by the mouth. The two functions frequently ascribed to it at one and the same time—namely, that of discharging the functions of a living tissue and that of serving as nutritive material for the tissues—are in-

compatible with each other. Life of the blood implies absence of nutritive value.

Under the conditions in which such experiments can best be made—namely, in starvation—the metabolism of the body is at its lowest. We shall see when we come to study the fate of the corpuscles after transfusion that starvation is particularly favourable to a lengthened stay of the red corpuscles in the circulation of their host. Hence it may be urged, and with some justice, that the more rapid destruction of blood when transfused under conditions more closely approximating those of health than the state of starvation, is, or may imply, a greater nutritive value of the blood under such circumstances than that above indicated. This is doubtless true; but in no case can the nutritive value be greater than that of a similar quantity given by the mouth, and

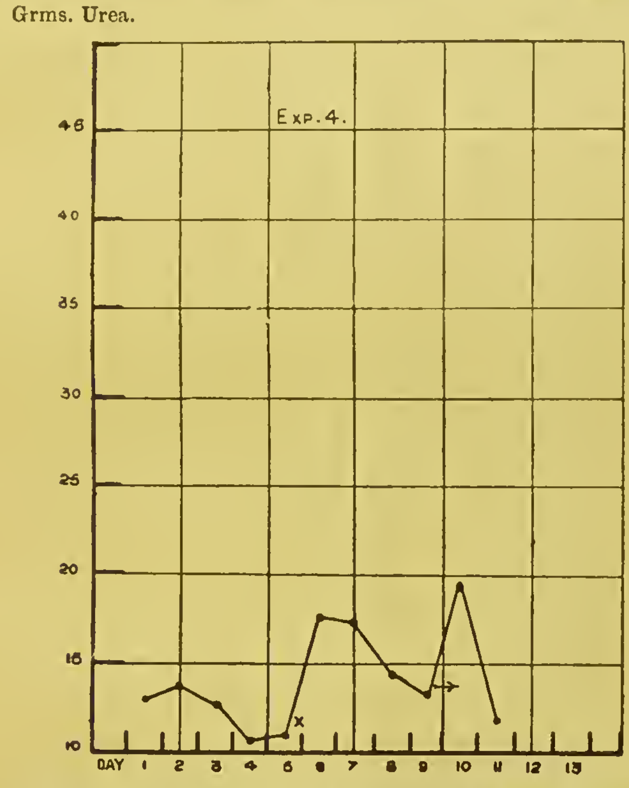

Fig. 3. ×=430 cc. Blood Serum transfused (6.88 grm, Nitrogen)
→=200 grm. Meat by the Mouth.

in the small quantities transfusible in man this is so small compared with that of the food required daily by the tissues, that it may be entirely overlooked. To transfuse blood on account of any nutritive properties it may be supposed to possess is an operation entirely devoid of any physiological basis. Hence we find that the loss of weight in starvation is unaffected by transfusion of blood in whatever quantities and however often repeated; and this is the case even although at death the blood may be not only increased in quantity, but actually richer in quality, than in health. Thus in one of Tchiriew's experiments in which transfusion had been repeatedly made, and in which the weight had fallen steadily from 6.928 to 4.583 kilos., the quantity of blood obtained from the body amounted to about 8.7 per cent. of the

body weight as compared with the 7 per cent. usually obtainable in health; and this blood contained 27.11 per cent. of solids with 4.21 grammes of nitrogen as compared with the 21 per cent. of solids containing about 3.2 grammes of nitrogen, usually found in healthy blood. Similar results were gained by Panum—by a method, however, not so free from objection as that of Tchiriew, on whose results, as on those of Forster, the greatest reliance can be placed.

What we have found to apply to pure blood applies in great degree to *defibrinated blood.* Its nutritive value is greater when given by the mouth than when transfused; this being due to the same cause, namely, that its red corpuscles—and they contain three-fourths of its organic constituents—continue to live for a certain time within the blood of their host. The slight rise in

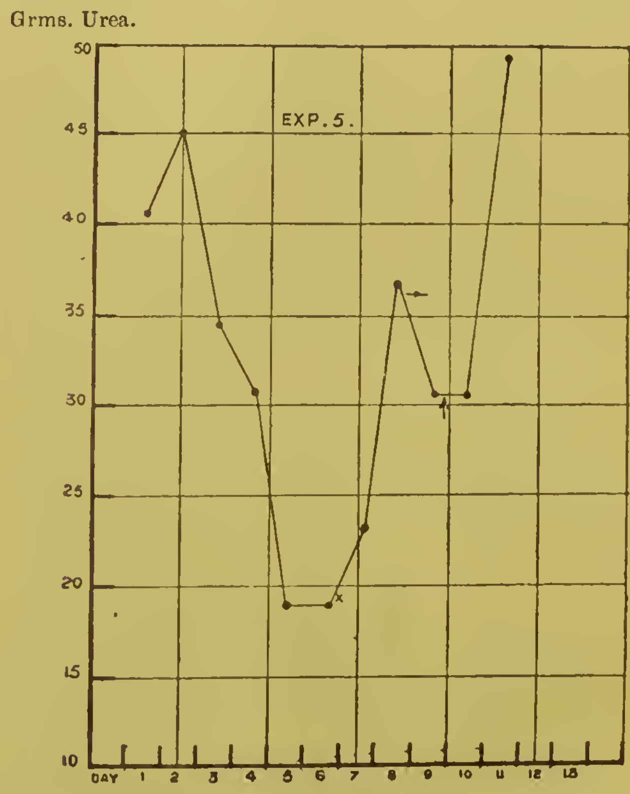

Fig. 4. ×=662 grm. Serum transfused (6.38 grm. Nitrogen).
→=600 grm. Meat by the Mouth.

the excretion of urea following on the injection of defibrinated blood is probably due to the disintegration of the proteids of the serum. This rise is never great, since the serum only contains a small percentage of organic constituents. In virtue of the change in the character of the proteids from the organised form in which they are present in the plasma to the unorganised form in which they are to be found in the serum, defibrinated blood may be regarded as possessing more immediate nutritive value for the tissues than pure blood; but this is so small that it may be neglected altogether.

Defibrination is often spoken of as harmless towards the blood; defibrinated blood is often regarded as blood minus its fibrin. Defibrination is indeed harmless towards a great number of the

red corpuscles, simply on account of their firmer periplastic structure. But it kills the plasma of the blood as certainly as the removal of myosin from muscle would be equivalent to its death.

The nutritive value of *blood serum* is the same whether given by the mouth or by injection into the blood-vessels (Figs. 3, 4, 5, and 6); but this is so small that the chief value of serum for transfusion purposes must depend upon its physical properties; and these are in no respect greater than those belonging to a corresponding quanity of neutral saline solution, such as ¾ per-cent. sodium chloride solution.

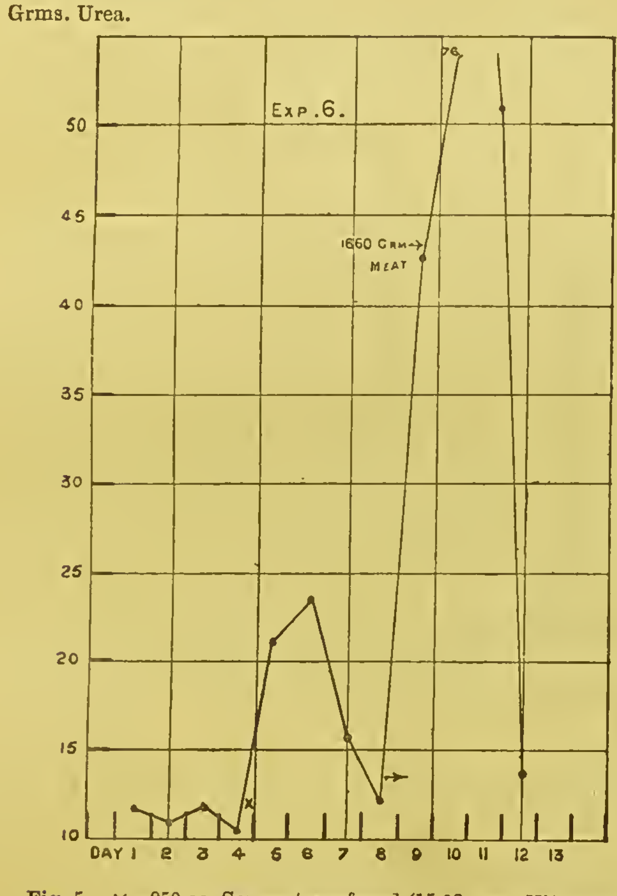

Fig. 5. ×=950 cc. Serum transfused (15.08 grm. Nitrogen).
→=500 grm. Meat by the Mouth.

Transfusion of pure blood is the transplantation of a living tissue made up of cellular elements floating in a fluid matrix. Transfusion of defibrinated blood is the transplantation of certain cellular elements, the red corpuscles, and also some white corpuscles, floating in a medium, the serum, which is not living. We might describe it therefore as the implantation of certain elements of a tissue into the living matrix of another tissue of the same kind, the plasma of the host's blood; the implantation being rendered possible by the resistant character of the red corpuscles and the fluid nature of their matrix. In either case the transfused blood has a respiratory value so long as the red corpuscles remain within the circulation of their host, and this is the only

respect in which it differs from or offers any immediate advantages over a corresponding volume of a neutral saline solution, since the small percentage of organic solids it contains apart from its red corpuscles serves but little nutritive purpose, and disappears in the course of a few hours.

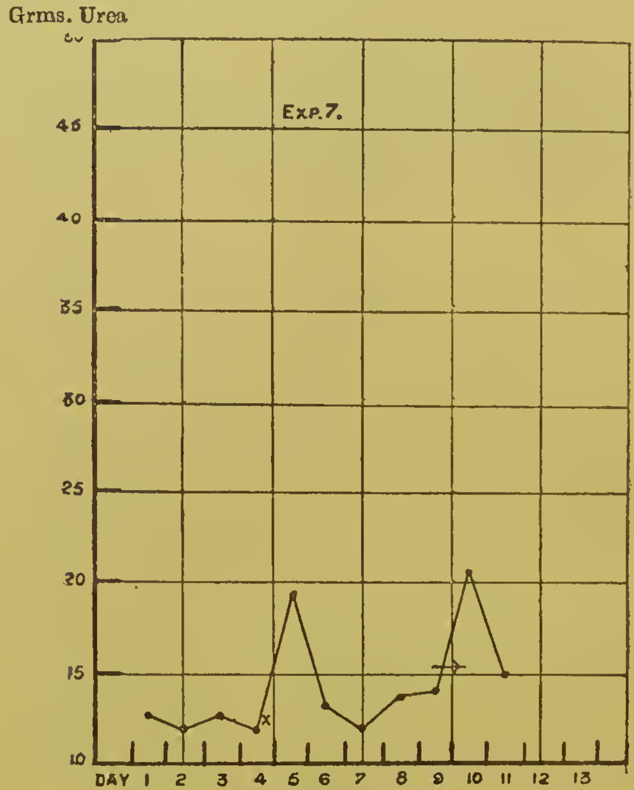

Fig. 6. × =522 grm. Serum transfused (30 grm. albumen).
→ =150 grm. Meat by the Mouth (32 grm. albumen).

LECTURE II.

RESPIRATORY PROPERTIES OF TRANSFUSED BLOOD.

Life Duration of the Red Corpuscles.—We have now to consider what value is possessed by transfused blood in virtue of the presence of the red corpuscles. So long as they remain within the circulation of their host, they will act as carriers of oxygen, and will thus have a certain respiratory value. What, then, is their life duration after transfusion? This subject I have discussed at length elsewhere.[1] After transfusion of large quantities of blood, there is a gradual and steady fall in the number of corpuscles till the normal is reached two to three weeks later. This lengthened life duration is only found when large quantities are injected, and only applies to rabbits. With smaller quantities the life duration is correspondingly shorter. In dogs a longer life duration than ten days was not observed. The two factors influencing it in all cases are—(*a*) the quantity of blood transfused; (*b*) the condition of the animal at the time of the transfusion and subsequent to it. As regards the latter, the following conclusions could be drawn from a study of the results obtained in the different experiments:

1. Any condition in which metabolism is diminished, as in starvation, tends to prolong the life of the red corpuscles. This applies both to the animal's own corpuscles and to the corpuscles of transfused blood (Fig. 7).
2. Any condition approaching that of health, in which metabolism is active, tends to shorten the life duration of the transfused corpuscles (Fig. 8).
3. In any condition in which metabolism is increased, the life duration of the red corpuscles is shortest of all (Fig. 9).[2]

The quantities of blood transfusible in man are so small that, under the most favourable conditions, the life duration of the red corpuscles is probably rarely longer than two to three days.

Effect of Defibrination.—Defibrination destroys the character of the blood as a tissue by destroying its matrix. On the red corpuscles, however, it has little or no injurious effect. Their life duration after defibrination is, under favourable circumstances, the same as when pure blood is transfused. (Fig. 7.) This con-

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[1] Life Duration of Red Corpuscles after Transfusion," etc., JOURNAL, i, 1887.

[2] For fuller discussion of these curves see my paper in *Journal of Anatomy and Physiology*, vol. xxi, 1887.

clusion is opposed to the one arrived at by Hayem, according to whom the corpuscles are by the act of defibrination doomed to a certain death—"are killed, beaten to death." So long as they remain within the circulation, they act as carriers of oxygen. They are ultimately destroyed as the animal's own corpuscles are, but that they are not killed is clear from the circumstance that they remain within the blood for days, sometimes even for weeks, whereas red corpuscles killed by the action of poisons—for example, by pyrogallic acid—are seized upon by the leucocytes and removed from the circulation in the course of a few hours.

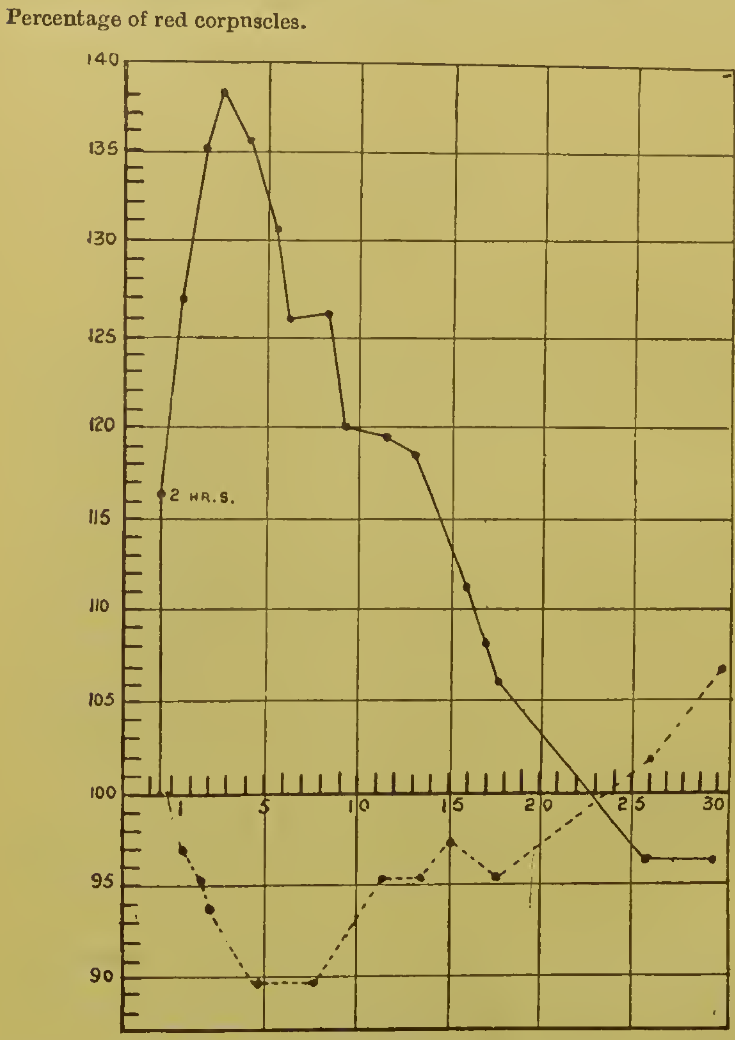

Fig. 7.—Life-duration of red corpuscles after transfusion of defibrinated blood into the peritoneal cavity (Experiment 10). The animal remained in good health throughout, although the original weight was not regained till close of the experiment. The weight is represented by the interrupted line.

Ultimate Fate of Transfused Blood.

The red corpuscles are thus the only elements of transfused blood that remain within the system for any length of time. After a time even they disappear. What becomes of them? Where and in what manner are they destroyed? Like all other tissues,

the blood must be affected by the discharge of its functions as the carrying tissue of the body. A certain wear and tear is connected with this process, which must affect in varying degree the various elements—plasma, white corpuscles, and red corpuscles.

Fate of the White Corpuscles.—The white corpuscles are most active during digestion. The changes in the blood at this time are, as we have seen, most marked within the portal blood and the organs connected with it. It is in this system that the changes in the leucocytes are also most marked at this period. There is an increase in their number, and their activity is otherwise shown

Percentage of red corpuscles.

Fig. 8.—Life-duration of red corpuscles after transfusion of pure blood into peritoneal cavity. The health of the animal exceptionally good throughout.

by the number and variety of the karyokinetic changes presented by their nuclei. Since increased metabolism implies increased disintegration, we should expect to find some evidence of this latter change in the blood. Such evidence is, I believe, to be found in the greater tendency of the portal blood to coagulate. After transfusion of blood, as my experiments show, it is not infrequent to find large compact thrombi in certain of the branches of the portal vein within the liver at periods varying from ten days to several

weeks after the transfusion. This thrombosis was found most marked when the destruction of blood had been most rapid. It was, in all probability, connected more particularly with the breaking up of the white corpuscles.

A similar thrombosis was found by Wooldridge to follow the injection into the blood of an extract he obtained from the lymph glands, testis, and thymus gland. The intravascular clotting was usually instantaneous and complete throughout the whole vascular system, causing sudden death; but under certain circumstances it was limited to the blood of the portal system. Wooldridge credited the leucocytes with but little share in this process; the "tissue fibrinogen," by whose union with the fibrinogen of the blood fibrin was formed, was derived from the lymph corpuscles, not from the leucocytes. I find no reason to believe that such a difference of structure or function exists between the leu-

Percentage of red corpuscles.

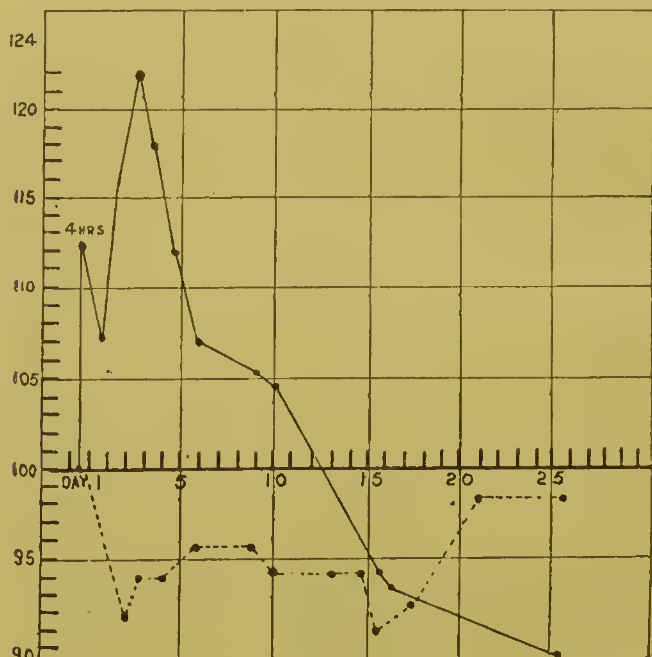

Fig. 9.—Life-duration of red corpuscles after transfusion of pure blood into peritoneal cavity (Experiment 9). The animal remained in poor health from the time of the experiment.

cocytes and the lymph corpuscles as Wooldridge supposed. Both of them are extremely active cells, and there is, therefore, some degree of probability in the view now advanced that the greater liability of the portal blood to coagulate both after transfusion and to a less degree in health is connected with the great activity and correspondingly greater disintegration of the cells, whether leucocyte or lymphoid, in and around the portal radicles. This conclusion is of some importance, as serving in part to explain the peculiar distribution of the thrombosis which so often occurs after transfusion of blood. The gastro-intestinal tract and the mesenteric veins are its chief seats.

Fate of the Red Corpuscles.—The evidence of any destruction of white corpuscles in health is thus but slight. The case is very different with the red corpuscles. The source of the bile pig-

ments is the hæmoglobin of the blood, and the daily excretion of these pigments points to the existence of some cause at work in the blood leading to a certain destruction of hæmoglobin, and presumably therefore to a certain daily destruction of red corpuscles. The first question which naturally arises is why there should be any such destruction. The *rôle* of the hæmoglobin in respiration is a comparatively passive one; the mere carrying to and fro of oxygen does not appear to demand the exercise of much functional activity, or necessitate very great metabolism on the part of the red corpuscles. Nevertheless, change is involved in this process. There is evidence that even if the sole function of the blood were respiratory, the red corpuscles would after a time become unfit for their work, relatively slight though it be. Their hæmoglobin cannot carry oxygen for an indefinite period. Hence it is that the outworn hæmoglobin has to be got rid of. The appearance of the red corpuscles in the animal scheme is contemporary with the appearance of an organ—the liver—one of whose special functions it is to remove pigment matters from the system.

When blood destruction is spoken of, we refer more particularly therefore to the destruction of the red corpuscles. What is the nature of this destruction? What are its seats, the agencies by which it is effected, and the conditions influencing it? The subject is one of no little complexity. In the following account, based on the results of a lengthened series of investigations, I shall confine myself to a consideration of such facts as bear more especially on the ultimate fate of the red corpuscles after transfusion.

The Nature of Blood Destruction.

Two forms of blood destruction are to be recognised, distinguishable alike by their character, the conditions influencing them, and their relative importance to the organism.

1. The first is a slow and gradual decay of the red corpuscle, manifested chiefly by changes in colour and shape, and its resistance to the action of reagents. The hæmoglobin remains within the corpuscle to the last, and becomes gradually converted into a globule of inert blood pigment, retaining the size and spherical shape of the red corpuscle. To this form of blood destruction I propose to give the name of *Passive destruction.* It is the mode of death of the red corpuscles which would occur were the blood subjected to no other changes than those involved in carrying on its respiratory functions. It is to a great extent independent of the action of cells. The final conversion of the hæmoglobin into effete blood pigment is, however, the result of the activity of cells. The chief evidence of passive destruction is the presence of pigment in certain organs of the body, chiefly in the spleen, capillaries of the liver, and bone marrow. The chief character of this pigment is the large and varying size of the individual pigment particles, and their irregular shape. This feature is best seen in animals in which the red corpuscles are normally very large; for example, in frogs and birds. The larger the animal's red corpuscles, the larger the pigment particles resulting from their passive destruction.[3] (Figs. 10 and 11.) When once formed this blood pigment is remarkably resistant to the action of reagents; it can be recognised long after the

[3] The pigment formed from extravasated blood or as the result of congestion presents the characters of that resulting from passive destruction. The description about to be given of this process has no reference to the occurrence of extravasation or congestion, the pigment resulting from which can at once be recognised by certain other features which need not here be specified.

death of the original red corpuscles. Hence the amount of pigment found in the organs specified affords a most reliable indication as to the amount of passive destruction that has occurred. Its absence from these organs can also be relied upon as showing that but little passive destruction has occurred—that the conditions have not been favourable to the persistence of the red corpuscles within the circulation for a sufficient length of time to allow them to undergo a process of natural decay.

2. The second form of blood destruction is one in which the hæmoglobin, instead of remaining within the red corpuscles, escapes frem them into the plasma, and is in great part excreted by the liver as bile pigments. To this form of blood destruction I propose to give the name of *Active destruction.* It is the change in the blood corpuscles caused by the action of water, various salts, etc. It differs from passive destruction in being closely dependent upon the activity of cells. The chief evidences of this active destruction are—(1) the formation of bile pigments by the liver, to which organ the

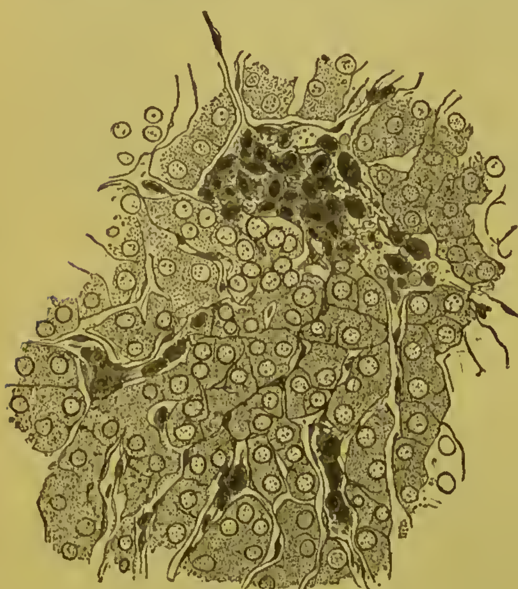

Fig. 10.

Fig. 11.

hæmoglobin is mainly carried; (2) to a less and altogether subsidiary extent in health, the formation of blood pigment. The chief character of this pigment is the small uniform size and spherical shape of its individual particles. (Figs. 12 and 13). The assumption of this form by the pigment is independent of the action of the cells; but the conversion of the hæmoglobin into blood pigment is as much the result of cellular activity as in passive destruction.

The size of the red corpuscles has no influence on the size of the pigment particles resulting from active destruction. It is the same in mammals as in birds or amphibians. The pigment is formed from free hæmoglobin.

No trace of blood pigment is usually found in the liver cells as the result of the breaking up in and excretion of this free hæmoglobin from the body. Under certain conditions of excessive active blood destruction in disease—for example, in pernicious anæmia—pigment may be found in great abundance in the liver cells; sometimes, also, in the capillaries of the liver. In both cases alike it possesses the features already described as characteristic of

pigment resulting from active destruction. The presence of this kind of pigment within the liver cells is in a special degree an evidence of excessive active destruction, and a further characteristic is that it is always most abundant in the liver cells of the portal zone of lobule. (Figs. 12 and 13.) Pigment resulting from passive destruction, however great it may be, is never found within the liver cells, but always lies enclosed in leucocytes within the capillaries, and it possesses the character belonging to pigment resulting from passive destruction. (Figs. 10 and 11.) This distinction is one of great importance. In the spleen and bone-marrow the character of the pigment is our only guide as to the nature of the blood destruction that has occurred. In the liver we have to consider not only the character of the pigment, but also its situation, whether within the liver-cells or within the capillaries.

Fig. 12.

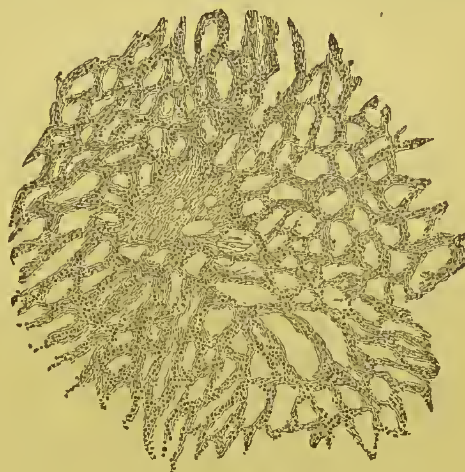

Fig. 13

Conditions Influencing Blood Destruction.

Age.—What is the relative amount of active and of passive destruction in health? It varies first of all according to the age. The spleen and bone marrow in young healthy animals—for example, in rabbits, dogs, cats—contain but little pigment. The amount of pigment tends to increase with age, and in old animals, especially in dogs, it may be found very abundant, not only in these two organs, but also in the capillaries of the liver. We must conclude, therefore, that in the young animal there is but little passive destruction; it is, indeed, at a minimum in young healthy animals, at a maximum in old animals. The significance of this is that in the former the conditions are not favourable to the slow and gradual decay of the red corpuscles; whereas, as age advances, the conditions become more favourable. With active destruction the very reverse is the case. It is greatest in youth, and diminishes gradually with advancing age. The proof of this is that the formation of bile pigments is most active in young and healthy animals; *and this process is entirely subserved by active destruction of blood.*. There is, in fact, no relation between the amount of passive destruction and the formation of bile pigments, a conclusion differing from that come to by previous observers (Quincke, Kunkel, Naunyn, and Minkowski). On the other hand, there is an extremely close relation between active destruction and the latter process.

Food.—The liberation of hæmoglobin from the red corpuscles in active destruction implies the existence of conditions unfavourable to the continued existence of the corpuscles. What are these? The first fact to be noted regarding them is that they are not in equal operation at all times. We have a guide to the amount of active destruction that occurs at any time in the quantity of bile pigments formed. In starvation the formation of bile pigments never entirely ceases, but it is at a minimum. In health it is much greater, varying, however, from time to time, according to the amount and quality of the food. It is greatest during digestion, and is most marked of all five or six hours after the ingestion of food. Since we cannot conceive of an increased formation of bile pigments without a correspondingly greater supply of hæmoglobin to the liver cells, we must conclude that the ingestion of food is followed by increased active destruction.

Seats of Blood Destruction.

Active destruction must therefore depend on certain changes in the blood, most marked during digestion. We have seen in our study of the physiology of the blood that the changes in the blood at this period are by no means great, and that any changes met with are most marked in the blood of the portal system, in the spleen, liver, and radicles of the portal vein.

Active destruction in health is almost entirely limited to the same system. The hæmoglobin set free is carried to the liver, where it is broken up and excreted in the form of bile pigments. The spleen is *par excellence* the seat of active blood destruction. The same structural features that favour the active destruction of red corpuscles—namely, slowness of circulation, closeness of relation of the cells of the pulp to the blood flowing through it, capacity for accommodating large and varying quantities of blood—favour also the seizure of red corpuscles in process of becoming effete by slow and gradual decay. The spleen is thus also the great seat of passive destruction. This circumstance explains the presence of blood pigment in that organ when it is entirely absent from the liver, a condition found in many of my experiments after transfusion. Next to the spleen the red bone marrow is the most important seat of passive destruction. It is the only tissue outside the portal circulation in which a destruction of blood of any consequence takes place. Within the liver the seats of active destruction are the capillaries.

The changes in the blood within the spleen, radicles of portal vein, and liver are compatible with the liberation of hæmoglobin in so small a quantity at a time, that it is impossible to recognise free hæmoglobin within the blood of the portal vein.

Active destruction of blood is not a mere physical process. It is not the result of the action of the constituents of the food on the red corpuscles, but is dependent on the activity of cells in the various situations in which it occurs, and on the changes in the plasma induced by this activity.

Summary.—The foregoing may be regarded as the first systematic attempt to bring the various facts connected with this subject into relation with one another. According to Voit, in Hermann's *Physiologie*, we have hitherto had no knowledge as to whether the corpuscles are destroyed in greater number in health than in starvation: "There is no reason why there should be a greater destruction of red corpuscles during digestion than during the fasting state." We have seen that it is precisely during digestion that the greatest and most active destruction of blood occurs. The greater

accumulation of pigment in the spleen and other organs in old age, in the fasting state, in conditions of wasting disease, is not an evidence of greater destruction of blood, but indicates that the conditions have been peculiarly favourable to the slow and gradual decay of the red corpuscles. In all these conditions blood destruction is at a minimum. The changes in the red corpuscles are most marked at the period of greatest activity of the leucocytes of the blood, and of the cells of the spleen and follicular tissue of stomach and intestine. The activity of these cells is regulated by the character and amount of the food given. With a rich supply of food their metabolism is greatest and the destruction of blood is also greatest. Since, however, with a rich supply of food the process of blood formation is most active, it follows that in the blood, as in all other tissues, anabolism and catabolism are closely associated. The conditions that favour its building up lead also to its breaking down. The final argument is thus supplied in support of the conclusion previously arrived at, that the blood is in all respects a tissue—in structure and behaviour, in its formation and its destruction.

Ultimate Fate of the Transfused Corpuscles.

The appearances presented by the various organs most intimately concerned—great accumulation of pigment within the spleen and bone marrow, its absence altogether from the liver, or presence in only slight amount within the liver-cells — point to the conclusion that their fate is precisely the same as that of the animal's own corpuscles. Transfusion of red corpuscles is a real implantation. Their destruction is effected in the same way and by the same agencies as in health. It is partly active, partly passive. The existence of the latter form of destruction is important, pointing as it does to the conclusion that the conditions may be so entirely favourable, that the corpuscles transfused are allowed to undergo a process of natural decay. The seats of their destruction are the spleen, the radicles of the portal vein, the capillaries of the liver, and the bone-marrow. The agencies by which this is effected are the same as in health.

Lastly, the conditions influencing its character and amount are the same ; it is specially affected by the amount and character of the food. Passive destruction is favoured by abstention from food, active destruction is favoured by increasing the supply of food. The bearing these conclusions have on the utility of transfusion will be seen when we come to consider the *rationale* of this operation. So far as transfusion of blood may be supposed to serve any respiratory purpose, any value it possesses depends on the life-duration of the red corpuscles, hence the importance of determining precisely what the most favourable conditions are for prolonging their existence within the circulation of their host.

Hæmogenic Properties of Transfused Blood.

Fate of the Hæmoglobin.—Its fate varies according as the destruction of the red corpuscles is active or passive. Passive destruction is conducive to the storing up of a large quantity of blood pigment within the body, chiefly within the spleen and bone-marrow. This pigment contains all the iron of the original hæmoglobin. Anything that tends to render destruction more active than passive favours the

removal of the hæmoglobin from the body in the form of bile pigments, and along with the bile pigments a certain proportion of the iron is always excreted in the bile. The chief advantage of having iron in the system is that it may afterwards be used for purposes of blood formation. This object is best served when the iron is deposited in the organs concerned in that process, namely, the bone-marrow, and to a less extent the spleen. The presence of iron in large quantities within the liver cells, as in some forms of anæmia in which the destruction is very active, does not serve any useful purpose. It is in process of excretion, and must interfere to some extent with the proper action of these cells.

Transfusion of blood may thus have a certain hæmogenic value in virtue of the presence of hæmoglobin in the form best suited to enable its iron to be stored up in the body. Free hæmoglobin introduced into the blood is removed at once as a foreign body; mainly by the kidneys, and in part also by the liver. Hæmoglobin introduced in the form of red corpuscles remains within the circulation for a period commensurate with the life duration of the corpuscles. Under favourable conditions, it is afterwards stored up in the spleen and bone-marrow in the form of blood pigment. Little or none of it is then removed from the system.

LECTURE III.

THE respiratory as well as the hæmogenic value of transfused blood is subject to the same conditions, and depends on the same two factors—(1) the quantity of blood transfused, (2) the nature of the blood destruction in progress at the time of the transfusion.

The greater the quantity of blood transfused, the longer are red corpuscles likely to remain within the circulation, and the more likely is their hæmoglobin and the iron it contains to remain within the system. Over this factor, however, we can exercise but little control. The quantity of blood transfusible in man can rarely be more than about 5 per cent. of the quantity of blood already in the body. And the life-duration of the red corpuscles under such circumstances is probably to be reckoned by a period of hours.

Of far more importance as a factor is the nature of the blood destruction at the time of the transfusion and subsequent to it. The more the blood destruction is " active," the shorter is the life-duration of the red corpuscles ; and how active this may at times be is evidenced by cases in which the transfusion is followed almost immediately by rigors, fever, and the appearance of free hæmoglobin in the urine. There are certain forms of anæmia in which excessive blood destruction is the essential feature, and these from their very nature are certainly unsuitable for transfusion. We shall presently see that it is possible for us to recognise by certain clinical features the nature of the anæmia we have to deal with, and in this way to avoid the operation of transfusion under circumstances that would probably render it of little, if any, service. In addition to these pathological variations, the activity of blood destruction is, as we have seen, subject to certain physiological variations chiefly having relation to the ingestion of food ; and this factor it is in our power to some extent to control by having regard both to the quantity and quality of food subsequent to the transfusion. Our object would be best attained by withholding food altogether, in this way rendering blood destruction, as far as possible, "passive." In any case the food should be as little nitrogenous as possible, since a nitrogenous diet undoubtedly increases blood destruction more than a simple carbohydrate one.

PHYSIOLOGICAL ACTION OF SODIUM PHOSPHATE.

It is by interfering with this—what may be regarded as the primary—indication in transfusion, namely, to reduce blood

destruction to a minimum, that the use of sodium phosphate for purposes of transfusion to prevent coagulation of the blood is attended with certain disadvantages that require here to be noted. First recommended now some years since by Dr. Braxton Hicks and Dr. Barnes, the use of this salt has recently been revived, apparently with much success, in the hands of Mr. Cotterill, Dr. John Duncan, and others.

This practice of mixing the blood with saline solutions before injection, and in this way getting rid of certain of the dangers incidental to the operation, is based on an assumption that is as erroneous as it is widespread, namely, that the behaviour of salts, poisons, etc., on the red corpuscles outside the body affords any clue to their probable behaviour on the blood after their injection. The conditions of an experiment outside the body and those existing within the body are entirely different. Outside, the conditions are physical; we mix the blood with the solution whose action is being studied, and allow the red corpuscles to remain at rest, and in contact more or less prolonged with the substance whose action is being studied under conditions that are entirely without parallel within the body. Within the body the conditions are physiological: the blood is constantly in rapid circulation; all the processes, including the process of blood destruction, are the result of the activity of cells, and may be modified in many ways by the action of the drug introduced.

The facility with which blood can be withdrawn from the body, and the action of drugs on its corpuscles studied, has led to many erroneous conclusions regarding the behaviour of various drugs on the blood. The following observations may serve to emphasise the above conclusions:—I have found a $\frac{3}{4}$ per cent. solution of sodium chloride to cause red corpuscles to break up and disappear in the course of twenty-four hours, while the same solution, after the addition of toluylendiamine in the proportion of $\frac{1}{2}$ per cent. to 1 per cent., preserved them intact for several days. The two observations were made at the same time, and the conditions were precisely the same in both.

Nevertheless, the injection of the simple saline solution into the circulation, even in the largest quantities, is harmless, while the injection of a few cubic centimètres of a 1 per cent. solution of toluylendiamine causes a most marked destruction of the red corpuscles, accompanied, it may be, by jaundice, hæmoglobinuria, or even death.

The bearing which these observations have on the value of the practice of injecting sodium phosphate with the blood transfused will be evident. Its behaviour towards the corpuscles outside the body affords no criterion of its probable behaviour after injection. In all cases bodies so introduced are in the position of foreign bodies. Their action will be harmless only on one condition—namely, that they affect in no way the activity of the cells of the blood on the one hand, or of the blood organs on the other. My observations show that in the case of sodium phosphate this condition is not fulfilled.

In every instance in which the salt was injected along with the blood, the subsequent blood destruction was of a more active character than that observed after transfusion of pure defibrinated blood alone, although the conditions of the experiments were precisely the same in all cases. (Fig. 14.) The evidence of this more active destruction was, in addition to the shorter life duration of the corpuscles as determined by enumeration (Fig. 14), of a twofold nature: 1. The presence of iron in the liver in larger amount than was ever observed in any experiment in which blood alone was transfused, the pigment in which this iron was con-

tained being found in the situation most characteristic of excessive blood destruction—namely, within the liver cells; and (2) an increase in the colouring matters of the fæces pointing to an increased formation of bile pigments.

Clinical evidence of a similar change in the character and amount of the bile excreted after transfusion is, I believe, afforded by an interesting case recorded by Dr. Halliday Croom.[1] On the day following transfusion of a mixture containing $5\frac{1}{2}$ ounces of

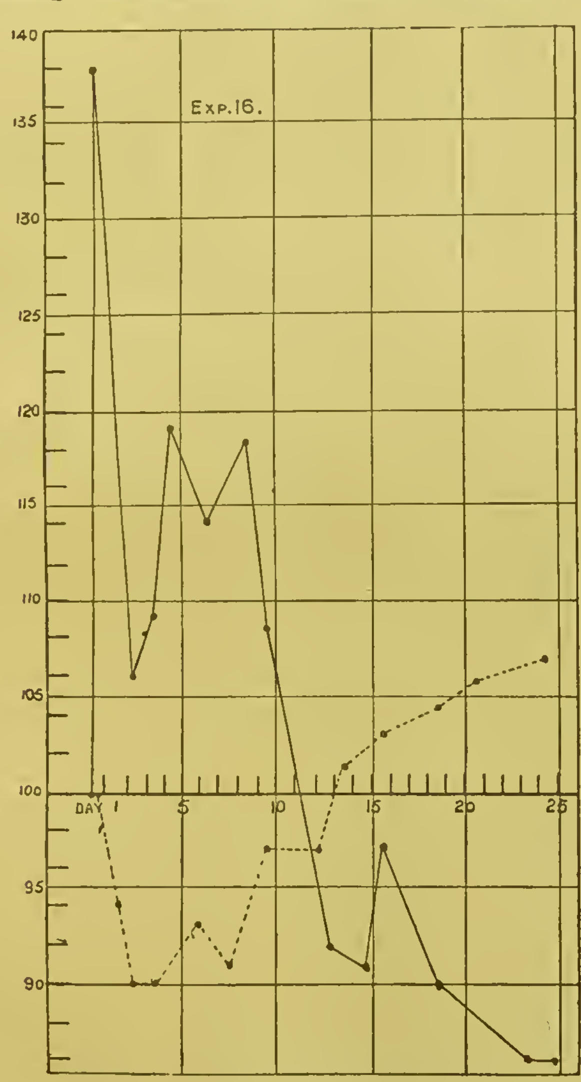

Fig. 14.—Injection of 100 cubic centimètres of blood and 30 cubic centimètres of a 5 per cent. solution of sodium phosphate into the peritoneal cavity of a rabbit, under the same conditions and with the same precautions as in the preceding series with pure and defibrinated blood. Greater quantity of blood transfused. Life-duration of red corpuscles shorter.

blood and $2\frac{1}{2}$ ounces of a 5 per cent. solution of sodium phosphate, there was a well-marked attack of jaundice. It is possible that the occurrence of the jaundice subsequent to the transfusion may have been a mere coincidence, but recent observations tend more and more to establish the importance and frequency of that form

[1] *Edin. Obstetric. Soc.*, June, 1887.

of jaundice depending on increased destruction of blood, sometimes termed "hæmohepatogenous," but whose essential feature, I believe, may be best described by terming it "hæmolytic." By far the best example of this form of jaundice is that so frequently met with in pernicious anæmia. The sudden onset of the jaundice in the above case after the transfusion, as well as its brief duration (it began to fade at once, and had disappeared at the end of a week), points in all probability to a causal connection of this kind between it and the injection.

The use of salts for purposes of transfusion is, to a great extent, based on the assumption that the composition of the plasma, as regards its richness in inorganic solids, is constantly varying, and that the injection of a little more or less is immaterial. So far is this from being the case that there is every reason to believe that its composition in inorganic solids remains, consistently with its discharge of great carrying functions, as constant as that of any tissue of the body.

This constancy in composition is most noticeable in the case of chlorides, which form more than one-half of the total percentage of salts in the ashes of the plasma, but it doubtless also applies to the other inorganic constituents. When a rich supply of chlorides is given in the food, the excess is at once excreted by the kidneys. When withheld altogether, the percentage in the blood at first falls very considerably, but ultimately rises again to the normal, while the excretion of chlorides by the kidneys falls to a minimum. The difficulty experienced in removing the chlorides from the serum by osmosis, even with the aid of large quantities of distilled water (Hoppe-Seyler), may be regarded as likewise pointing to the same conclusion—namely, that the inorganic solids of the plasma, as of the red corpuscles, are present, not in free form as such, but in combination with the other constituents. They must be regarded, therefore, as constituting portions of an organised structure built up by the agency of cells, and their amount is, therefore, solely regulated by the activity of these cells. This is specially true of the phosphoric acid of the blood, a considerable part of which is derived from the phosphorus contained in lecithin, one of the most complex, as it is one of the most widely spread, organic compounds in the body. It is also true of the sulphates, some of which are derived from the sulphur of proteids. Hoppe-Seyler has, within the last few weeks, shown that even the hæmoglobin of the corpuscles is not present in the corpuscles as such, but is in intimate combination with other organic and inorganic solids.[2]

The importance of these various facts and observations lies in this, that they point clearly to the conclusion that all salts injected directly into the blood form no part of the blood while present, but are in the position of foreign bodies. They are removed from the blood and excreted from the body with the same rapidity as sugar, peptones, hæmoglobin, and large quantities of neutral saline solutions when similarly injected.[3]

Pathology of Transfusion.

Thrombosis.—Transfusion of blood is an operation at all times attended with certain dangers that fully entitle it to the respect

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[2] For independent evidence pointing strongly to the same conclusion, see *Lancet*, ii, 1888, p. 656, where I have described a special variety of hæmoglobinuria characterised by the excretion of hæmoglobin not in free form, but in combination with albuminous constituents of the blood.

[3] St. Klikowicz. "Die Regelung der Salzmengen de Blutes." *Archiv f. Physiologie.* 1886. P. 818.

with which it is generally regarded, notwithstanding that the operation is one attended with no great technical difficulties.

Up till 1821, the operation of transfusion consisted in the injection of pure blood. In that year attention was drawn for the first time by two French observers (Dumas and Prévost) to the fact that transfusion of defibrinated blood was equally efficacious in rescuing animals from impending death from hæmorrhage. Their observations were confirmed a few years later by Dieffenbach (1828); but the use of defibrinated blood gained ground so slowly that up till 1860 only 13 cases had been recorded.

The great impetus to its use was given by the researches of Panum (1863). Undeterred by Magendie's experiencies as to the dangers accompanying the transfusion of such blood, Panum advocated transfusion of defibrinated blood to the entire exclusion of pure blood, urging as one of its advantages that large tanks of it could be kept ready for use on the field of battle. These were, in truth, the palmy days of transfusion.

The disturbances noted by Magendie following the transfusion of defibrinated blood were chiefly the appearance of blood-stained froth at the nose and mouth, œdema and congestion of the lungs, subpleural hæmorrhage, swelling and congestion of the mucous membrane of stomach and intestine, with occasionally the presence of blood in the fæces, and were ascribed by him to an alteration in the viscosity of the blood from the removal of the fibrin. Panum met with similar changes in a number of his experiments; but he attached no importance to them, considering them merely as the result of the rupture of certain of the capillaries from increased action of the heart after the transfusion. Ponfick and Landois, who also met with them, explained their occurrence in different ways; the former regarding them as the result of irregularities in the mode of injection, the latter as the result of blocking up of certain capillary districts with "fibrin-stroma"—the stromata of the injected corpuscles—and the subsequent rupture of adjacent capillaries. None of these explanations serve in any way to account for these various pathological changes.

With regard to the last one more particularly it may be noted that it is possible, as I have found, by means of destructive agents injected into the blood, to reduce the greater number of the red corpuscles to the form of stromata, and to have them circulating in the blood for days without producing any of the disturbances which may sometimes be caused by the injection of a few drops of blood.

The observations that threw most light on the true nature of these disturbances were those of Armin Köhler (1877). The various pathological changes, with their accompanying symptoms, are the results of a widespread capillary thrombosis in various parts of the body, occurring more especially, however, in the capillaries of the lungs and gastro-intestinal mucous membrane, occasionally also in the mesenteric veins and mesenteric glands, sometimes throughout the entire blood vascular system.

The conditions favouring the occurrence of this thrombosis are still in great part unknown. Defibrinated blood obtained by allowing the blood to coagulate spontaneously, and then pressing out the clot, was found by Köhler to be much more active in inducing thrombosis than that obtained in an ordinary way by a process of whipping. The great feature of defibrinated blood in all cases, however obtained, is the uncertainty of its action. It is sometimes quite harmless, at other times highly dangerous, this result being entirely independent of the quantity injected or the

care taken in injecting it. The same uncertainty in action applies, although perhaps in less degree, to all blood after its withdrawal from the vessels.

Pathological Action of Sodium Phosphate.

Nor is this peculiarity in the behaviour and uncertainty in action of blood affected in any degree by the use of such salts as sodium phosphate.

The two following experiments may serve to illustrate both the harmlessness of such transfusions and also the dangers they may occasionally be attended with. They will at the same time serve to show how entirely independent the disturbances are of any factors such as overfilling of the system of the blood or too rapid injection, the factors so frequently credited with their production.

Experiment 13.—*Auto-transfusion.* Rabbit anæsthetised with ether. Twenty cubic centimètres of blood withdrawn from one of the carotid arteries into a vessel containing 15 cubic centimètres of a 5 per cent. solution of sodium phosphate maintained at the temperature of the body; immediately allowed to flow back into the jugular vein. The injection completed without the slightest disturbance of any sort arising.

Experiment 14.—*Auto-transfusion.* Rabbit anæsthetised with ether. Twenty cubic centimètres withdrawn from carotid artery into 20 cubic centimètres of a 5 per cent. solution of the same salt kept at the body temperature. Blood was immediately reinjected into the jugular vein, with the fullest precautions; my object in doing the experiment being to reinject the whole of the blood back into the circulation. Immediately the blood began to flow the animal became restless and uneasy, its breathing more rapid, and it began to struggle. The injection was stopped, and then resumed after a short pause, the symptoms having apparently passed off. Violent convulsions then immediately set in, the breathing became extraordinarily rapid, a large quantity of frothy blood-stained mucus poured from nose and mouth, and death occurred five minutes after the injection had been commenced and after the injection of 7 cubic centimètres of blood (2 drachms).

An examination made at once revealed the following *post-mortem* changes. Both ventricles of heart distended and motionless, the auricles only moderately distended and still beating. A small quantity of serum within the pericardium. The ventricles on being opened began again to beat, and were both found filled with a firm compact thrombus, red in the left, of darker colour in the right ventricle. In both cases the thrombus extended back into the auricles, and could be traced from the left auricle into the smaller branches of the pulmonary veins. The thrombi were not however continuous, but were in isolated portions of more or less cylindrical shape, tapering off at each end. From the ventricles the thrombi also extended foward into the aorta and into the pulmonary artery, and in the former they could be traced as low down as the descending thoracic aorta, where they gradually tapered off.

The lungs were extremely œdematous, especially at their bases, the bronchi and trachea contained much frothy blood-stained mucus. Over the surface of the lungs were numerous bright red subpleural hæmorrhages.

The ventricles began to beat as soon as they were cut open, and the heart only ceased to beat when cut out of the body some ten minutes after death had occurred.

There could be no doubt in this instance as to the significance

of the symptoms which preceded death, and the pathological changes which underlay them. The peculiarity of the thrombosis was that it was complete, extensive, and widespread. The shape of the thrombi in the lung showed that thrombosis had occurred independently at different parts, and had not extended out from one centre. The individual thrombi were remarkable for their extreme toughness. Microscopic examination showed that they were specially numerous in the smaller arterioles and capillaries of the lung. The distribution of the thrombosis in the portal system was, unfortunately, not noted.

In the light of these observations the various disturbances so frequently met with during the performance of transfusion acquire a new significance and importance. The sudden gasping for breath, or the quick and laboured breathing, the feeling of tightness and oppression over the chest, or of precordial anxiety, the forcible cardiac action, or the threatened failure of heart and great weakness of pulse, the restlessness and distress from pains in loins and abdomen, with urgent calls to stool, and the vomiting, these and other symptoms are undoubtedly the manifestation of changes in all respects similar to those found in animals under similar circumstances. Köhler, indeed, found that in animals killed while showing similar symptoms of distress, small thrombi could be discovered in the capillaries of the lungs and gastro-intestinal mucous membrane, sometimes in the mesenteric veins.

I have frequently found changes of less degree (numerous subpleural hæmorrhages) after the transfusion of 10 or 20 cubic centimètres of an animal's (rabbit's) blood into its own peritoneal cavity —under circumstances, therefore, that entirely precluded the operation of any factors such as the introduction of air, too hasty injection, or overfilling of the system.

The following cases of Quincke may serve to illustrate the nature of the dangers attending transfusion of blood.

Cases of Pernicious Anæmia.—Arterial transfusion of 85 cubic centimètres of defibrinated blood. Towards end of the transfusion face became flushed and covered with perspiration, followed suddenly by pallor and complete collapse. Heart sounds inaudible; pulse not to be felt. Under influence of irritants and stimulants, recovery, but great complaint of cold during the next three hours, with violent abdominal pains and diarrhœa. Urine passed the same day albuminous, and contained a considerable quantity of free hæmoglobin, with casts. The temperature, which before the operation was 98° F., rose in the course of four or five hours to 102°, falling again in the evening to 98.5°.

In another case (Case XII), in which 50 cubic centimètres of defibrinated blood were injected, the transfusion had to be stopped on account of the feeling of great anxiety on the part of the patient with sickness. Half an hour later there was a rigor, which lasted three to four hours, violent pains in the abdomen, and repeated urgent calls to stool lasting several hours. The temperature, which before was 99° F., rose in the course of two hours to 102.4°, and seven hours later still remained at over 100°.

In a third (Case XV), in which 105 cubic centimètres of defibrinated blood were transfused, there was diarrhœa, and icteric tinge of conjunctivæ became more marked.

In another (Case XVI) transfusion of 100 cubic centimètres of defibrinated blood was followed by giddiness and rigors, pulse rose from 84 to 160, temperature to 102°, and in the course of two hours there were no fewer than six loose motions into the bed, urine became albuminous, and contained free hæmoglobin with numerous hyaline and granular casts.

The use of sodium phosphate along with the blood is not unat-

tended with dangers of similar nature; "unpleasant though evanescent symptoms," great distress from pain in loins, and forcible cardiac action, were observed by Dr. Duncan in a case of pernicious anæmia after the injection of 4 ounces of a mixture of blood and sodium phosphate, and were ascribed by him to the too rapid injection of so much blood at a time "when the quantity of blood was daily increasing." As has been seen, the same train of symptoms may follow the injection of a few cubic centimètres of the animal's own blood, and may be absent after the injection of fluid to the amount of 100 per cent. or 130 per cent. of the quantity of blood in the body (Lesser).

There can, I think, be little doubt that their cause is to be sought in changes in all respects similar to those found in animals—in the occurrence, namely, of capillary thromboses, the pains felt being probably due to spasm. It will be noted how constantly the abdominal pains are met with, usually attended by diarrhœa more or less severe. In this connection it will be remembered that the radicles of the portal system within the gastro-intestinal wall have been seen to be the favourite seat for the occurrence of such thromboses, and the subsequent swelling and congestion of the mucous membrane, so well described by Magendie in the first instance, are doubtless responsible for the violence of the symptoms observed, pains, diarrhœa, appearance of blood in stools, etc. Sometimes, though rarely, the effect of transfusion in causing intra-vascular clotting may be observed in a still more striking way, as in the case recorded by Hayem,[4] in which, immediately after a transfusion, phlegmasia alba dolens appeared, first in one leg, then in the other. The condition of the vessels and their blood was probably such that it never required the extra stimulus afforded by the transfused blood to bring about instantaneous clotting.

The cause of thrombosis in all such cases is by no means clear. It is probably connected with the disintegration of the white corpuscles of the injected blood as well as of the plasma, and is favoured doubtless by certain conditions of the blood of the recipient at the time of the transfusion. The frequency with which the characteristic symptoms are met with in cases of pernicious anæmia is doubtless connected with the excessive blood destruction, with consequent instability of the blood, which characterises that disease. With regard to the action of sodium phosphate, one of the favouring conditions we may judge to be the quantity of the solution injected. In the experiment already recorded the blood and salt solution were mixed in equal proportions, instead of in the usual proportion of 3 to 1. It is possible that the influence of this factor is also to be observed in one of Dr. Duncan's cases, in which the patient suddenly became nearly collapsed; the salt solution had, by an oversight, been made of the strength of 10 per cent. instead of 5 per cent.

Fever and hæmoglobinuria not infrequently follow transfusion of blood. They are of constant occurrence when the blood of one animal is transfused into another of different species. In all cases the occurrence of hæmoglobinuria is of the greatest significance as marking—(1) the sudden and rapid liberation of the hæmoglobin from the injected corpuscles, but still more as pointing (2)[5] to the seat of this liberation, namely, the general circulation. In health no such liberation ever occurs in the general circulation. Active destruction, as I have shown, is limited to the portal circulation—chiefly to the spleen: the hæmoglobin set free being disposed of by the liver before it reaches the general circulation.

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[4] JOURNAL, vol. i, 1884, p. 387.
[5] Hunter, *Lancet*, vol. ii, 1888.

The largest quantities of blood may under ordinary circumstances be transfused from one animal into another of the same species without the occurrence of any hæmoglobinuria. The explanation of this is, as we have seen, that the seats of destruction are the same as in health.

The appearance of hæmoglobin in the urine is an indication therefore that the conditions of the blood within the general circulation are entirely inimical to the preservation of the red corpuscles, even for a few hours.

The rigors and fever which mark this occurrence are connected with the liberation of the hæmoglobin. The same phenomena attend the liberation of hæmoglobin in paroxysmal hæmoglobinuria.

Any value which blood transfusion possesses over the infusion of saline solutions, we have seen, depends upon the presence of the red corpuscles and their hæmoglobin in the general circulation. We now find that the chief dangers of transfusion are connected with the presence of the white corpuscles of the injected blood and from changes in the white corpuscles and plasma of the recipient's blood.

Any advantages that transfusion of red corpuscles may have over simple saline injections are counterbalanced by the dangers attending the simultaneous injection of the white. In the case of defibrinated blood the latter so preponderate that transfusion of defibrinated blood is an operation not only dangerous in itself, but one whose practical value by no means serves to compensate the additional risks run in carrying it out.

Practice of Transfusion.

We have up to this point considered transfusion as partly a physiological, partly a pathological, problem. It is not in health, however, in which condition we have been hitherto studying it, but in disease, that transfusion finds its practical application.

We have seen that transfused blood (1) possesses no nutritive value. Transfusion of blood is, therefore, useless in all forms of "atrophic" anæmia, by which term rather than by the unfortunate term "symptomatic," hitherto given, I would distinguish all forms of anæmia in which the changes in the blood simply correspond in degree to the wasting changes occurring in other tissues. The anæmia of all forms of wasting disease is, therefore, of this character. It is important to note that the degree of anæmia cannot be judged of by the amount of pallor. Examination of the blood alone enables us to determine whether the anæmia is "atrophic" in its nature or not.

(2) If the condition to be met is a want of red corpuscles, or an incapacity on the part of those already present to carry on their respiratory functions, then transfusion of blood may possibly be of value. The red corpuscles transfused remain for a certain time within the circulation of their host. Transfusion of blood may conceivably be of value in carbonic oxide poisoning, where the red corpuscles are incapacitated for their work by a close union of the gas with the hæmoglobin of the corpuscles. Successful cases have been recorded without, however, any clear demonstration, that the most dangerous stage of the poisoning had not been passed before the operation was performed. In most of the cases recorded, chiefly by German observers, the transfusion was not made for many hours after the symptoms of poisoning were fully developed. In any case the transfusion must in this instance always be preceded by a venesection. Even when this is done, the operation is of doubtful value.

As regards the other indication for the transfusion of red corpuscles—the existing want of them—it may be stated that there is scarcely a single condition of the blood in which the want of red corpuscles is a source of urgent danger. After the greatest losses of blood in animals, a sufficient number of red corpuscles always remain in the circulation to carry on respiration, provided that the circulation is maintained. In animals, after loss of half to two-thirds of the total quantity of blood in the body, the number of corpuscles per cubic millimètre may be found as high as 3,000,000 or 4,000,000. The absolute loss is, of course, great, but the relative loss is slight, and is of little importance. The animal's health is in no way affected injuriously by the loss. In some of my experiments the animals have gained in weight from the day of the abstraction of blood, no indication being afforded of any disturbance at all, except on examination of the blood, which showed the reduction in the number of corpuscles. In man the loss of blood can never be so great as in animals. Syncope occurs earlier. Transfusion of blood is, therefore, never required for the purpose of supplying red corpuscles to carry on respiration after sudden loss of blood in a patient previously healthy. The immediate source of danger in such cases is not the want of red corpuscles, but the disturbance of the relation between the vascular system and its contents.

Nor is transfusion of blood indicated on account of its respiratory value in anæmia of idiopathic or traumatic origin. By idiopathic anæmia I mean those conditions in which the changes in the blood are in excess of the changes in the other tissues, and constitute a characteristic feature of the disease. The best examples of this form of anæmia are pernicious anæmia, chlorosis, and leucocythæmia. It is remarkable how slight the disturbance in respiration may be in cases, for example, of pernicious anæmia in which the red corpuscles may be reduced to 10 per cent., or even less, of their original number. I have observed cases in which the number of corpuscles was as low as 500,000 or 600,000 per cubic millimètre, instead of 5,000,000 as in health, the respirations never rising above 20 per minute; the breathing perfectly tranquil throughout. The great breathlessness on exertion always observed depends on other factors, and in any case never constitutes an indication for the performance of transfusion.

(3) If the condition to be met is a failure in blood formation due, perhaps, to the want of iron in the system, transfusion of blood may be of some value, in so far as we in this way supply the organism with iron in the form in which it can most conveniently be stored up in the body. The two conditions in which this disturbance is most marked are chlorosis, and traumatic anæmia resulting from long-continued and repeated hæmorrhages. There is, I conceive, no disease in which transfusion of blood corpuscles is theoretically more indicated than in chlorosis. The anæmia here is in a special degree the result of an insufficiency of iron in the system, so much so that a chlorosis of old age where, as we have seen, the tendency is for pigment to accumulate in great abundance within the spleen, bone marrow, and other organs, is almost a contradiction in terms. The anæmia of chlorosis we can, however, readily combat without having resort to transfusion.

The question as to the advisability of transfusion in traumatic anæmia is not so easily answered. Our object here is not so much to relieve any passing danger arising from insufficient bulk of fluid, or want of red corpuscles, as to stimulate blood formation. That transfusion appears to be of value in some cases there is no reason to doubt, but how far the result is *propter hoc* as well

as *post hoc* it is impossible in any case to determine. If it really is of any value it must be solely by assisting blood formation. I am inclined, however, to regard it of doubtful value even from this point of view, and that for the following reason: that in animals the subsequent recovery after loss of blood is certainly not accelerated by transfusion of blood, but in most cases is actually retarded (Hayem, von Ott). If this be the case where the blood-forming organs are active as in health, it is difficult to understand how the result will be different in disease. The recovery is effected with greater rapidity when simple saline solution (3 per cent. solution of common salt) is injected than when blood is transfused. My own experiments show that the recovery after infusion of saline solution is remarkably rapid. The time required for the return of the red corpuscles to their original number after loss of blood, without subsequent infusion or transfusion, varies from two to three weeks. With subsequent infusion of simple saline solution it is the same; whereas with subsequent transfusion of blood complete recovery is delayed a week longer or more. Further, what is perhaps more striking and certainly is of more importance, is the fact that during the subsequent recovery the animal generally appears to be in better health after infusion of salines than after transfusion of blood.

Even in traumatic anæmia resulting from long-continued losses of blood, transfusion of blood has in all probability no value not possessed by simple saline solution. The former may actually retard blood formation; the latter is at least always harmless, and might be beneficial if it were required.

In the other forms of idiopathic anæmia, pernicious anæmia, and leucocythæmia, transfusion of blood can, in my opinion, never be indicated. In both, the condition of the blood is the result of changes in the blood-forming or blood-destroying processes, or in both.

In leucocythæmia the disturbance is one of blood formation in the first instance, evidenced by the increase in the leucocytes of the blood, while the diminution in the number of the red I find to be due in great part to excessive blood destruction, probably induced by the activity of the leucocytes. In pernicious anæmia, the condition of the blood is mainly the result of excessive destruction. Transfusion of blood under such circumstances is not unattended by dangers as we have seen, but is followed in most cases by rapid destruction of the injected red corpuscles as evidenced by fever, sometimes by hæmoglobinuria, occasionally also by increase in the slight icterus which so frequently marks the progress of the disease.

It is important therefore to be able to distinguish between profound anæmia of traumatic origin and pernicious anæmia; and this I find it is possible most easily to do, by having regard to the character of the urine in the two cases. I find that the urine of pernicious anæmia contains large quantities of pathological urobilin, recognisable both chemically and on spectroscopic examination, and that its colour is correspondingly high. In marked cases, or during periodic exacerbation of the destructive process within the blood, this character of the urine is a very striking one; more especially as it is unaccompanied by any diminution in the quantity, is frequently quite independent of the occurrence of fever, and the specific gravity is usually very low (1010 to 1015).

The urine of traumatic anæmia, on the contrary, is exceedingly pale in colour, and is free from pathological urobilin. If in addition we note the condition of the blood in the two forms of anæmia, with special reference to the relation between the richness

in hæmoglobin and the corpuscular richness—in traumatic anæmia the percentage diminution in hæmoglobin being usually considerably in excess of the diminution in the number of corpuscles; whereas in pernicious anæmia the hæmoglobin percentage is always relatively high, I believe we shall be able in future to draw a sharper line of distinction between these two forms of anæmia than has hitherto been possible.

(4) Lastly, if the condition to be met in transfusing blood is a threatened failure of circulation as the result of sudden loss of blood, then it is unnecessary to have recourse to blood transfusion, as infusion of any neutral saline meets equally well, if not better, all the indications. The value possessed by transfused blood in such cases is almost solely in virtue of its physical properties. The chief physical property of blood for purposes of transfusion is undoubtedly its volume. The immediate source of danger from sudden loss of blood is the fall in the blood pressure to a point where the circulation is unable to be maintained. The obvious indication, therefore, is to raise the pressure within the vessels. In health the blood pressure is dependent mainly upon peripheral resistance. The effect of a loss of blood on the blood pressure is, up to a certain point, completely neutralised by an increase in the peripheral resistance due to stimulation of the vasomotor centre. It is only after very severe hæmorrhage that this relation between the vessels and the amount of fluid they contain necessary for the carrying on of the circulation is disturbed. The pressure falls rapidly and suddenly, and death will ensue unless means be taken to meet the threatened failure of the circulation. The readiest way in which this can be done is to replace the lost blood with a certain bulk of fluid. To meet the danger thus arising, the quantity of blood is of more importance than its quality. In an emergency the infusion of ordinary water (Coates) has been followed by results as successful as any ever obtained after transfusion of blood. Bulk for bulk, pure or defibrinated blood, however, must possess certain advantages over neutral saline solutions free from organic constituents. They doubtless possess a certain physiological value as well as a physical value, inasmuch as blood must have a greater and more immediate effect in restoring the tone of the vasomotor centres than saline solutions. These advantages, however, are more than neutralised by the other and still greater disadvantages—namely, (1) the difficulty of obtaining blood in sufficient quantity or with sufficient rapidity as compared with the ease with which simple saline solution can be prepared; (2) the dangers attending the transfusion of blood, compared with the absolute freedom from danger possessed by solution; and (3) the doubtful value of the transfusion, whether hæmogenic or physical, when compared with saline solution.

Transfusion of blood will long continue to be practised, and its action studied on account of the many interesting problems connected with the physiology and pathology of the blood on which it is well fitted to throw light. For practical purposes, however, all the advantages to be gained by transfusion may, I believe, be equally well and more readily obtained by infusion of a neutral saline, such as ¾ per cent. solution of common salt (about one drachm to the pint). The only pressing indication for the performance of transfusion is the collapse from sudden and severe loss of blood.

With regard to its performance, two points may be noted: (1) that the simpler the instruments used—a simple glass cannula, with a piece of india-rubber attached, and a clean syringe—the more easily will this infusion be effected, and the less likelihood

will there be of the injection of air—a source of danger to which far too much importance has long been attached, as it is also one which can readily, with a little care, be altogether avoided; (2) that the temperature of the solution should never rise above that of the body.

Under no circumstances is transfusion of milk or of other mixtures possessing what are supposed to be nutritive properties, ever indicated. They possess no value not possessed by an equal bulk of saline solution.